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# Health Effects Assessment for Chlorobenzene

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# HEALTH EFFECTS ASSESSMENT FOR CHLOROBENZENE

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TABLE 3-1 (cont.)

| Species | Dose (mg/kg/day) | Duration (days) | Effects | Reference |
|---|---|---|---|---|
| Rat | 42.9 | 13 weeks | none | NTP, 1983 |
| | 89.3 | 13 weeks | none | |
| | 178.6 | 13 weeks | minimal centrolobular hepatocellular necrosis | |
| | 357 | 13 weeks | decreased body weight gain, increased GGTP and alkaline phosphatase in females, increased excretion of porphyrins, centrolobular hepatocellular necrosis, nephropathy in males, myeloid depletion of bone marrow | |
| | 538 | 13 weeks | decreased body weight gain and survival of animals, hematologic effects, increased GGTP and alkaline phosphatase in females, polyuria in males, increased excretion of porphyrins, centrolobular hepatocellular necrosis, nephropathy, lymphoid depletion of thymus and spleen, myeloid depletion of bone marrow | |

## DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with chlorobenzene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Chlorinated Benzenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-028. NTIS PB 81-117392.

U.S. EPA. 1982a. Hazard Profile for Chlorobenzene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Health Assessment Document for Chlorinated Benzenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-015F. NTIS PB 85-150332.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, $q_1^*$s have been computed based on oral and inhalation data if available.

## ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The liver and kidneys appear to be target organs for chlorobenzene toxicity. Three separate subchronic oral exposure studies (one in dogs, two in rats) define comparable NOELs. The observed adverse effects indicated a higher sensitivity of the dog to chlorobenzene than the rat. Based on these findings, the highest NOEL of 27.3 mg/kg/day from the dog study (Monsanto, 1967a) was considered appropriate to derive an ADI. The estimated AIC is 1.9 mg/day, estimated by applying an uncertainty factor of 1000. This estimate may be considered to provide adequate protection against adverse human health effects. Long-term (lifetime) animal exposure data are needed to better characterize the toxicity of this compound. A CS of 8 was calculated for the low blood sugar levels, vomiting, diarrhea and conjunctivitis observed in dogs at 55 mg/kg/day.

Subchronic inhalation data from several species are available, but chronic inhalation exposure assessments for chlorobenzene are lacking. A AIC for inhalation exposure has been estimated based upon the lowest subchronic LOAEL reported (75 ppm) (Dilley, 1977). This AIC, 0.4 mg/day, may be conservative. More experimental data are needed addressing lower concentrations and longer durations of exposure to more completely characterize chlorobenzene toxicity.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADI | Acceptable daily intake |
| AIC | Acceptable intake chronic |
| AIS | Acceptable intake subchronic |
| BCF | Bioconcentration factor |
| CAS | Chemical Abstract Service |
| CNS | Central nervous system |
| CS | Composite score |
| DNA | Deoxyribonucleic acid |
| GGTP | γ-Glutamyl transpeptidase |
| LOAEL | Lowest-observed-adverse-effect level |
| MED | Minimum effective dose |
| NOAEL | No-observed-adverse-effect level |
| NOEL | No-observed-effect level |
| ppm | Parts per million |
| $RV_d$ | Dose-rating value |
| $RV_e$ | Effect-rating value |
| SAP | Serum alkaline phosphatase |
| SGOT | Serum glutamic oxalacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| STEL | Short-term exposure limit |
| TLV | Threshold limit value |
| TWA | Time-weighted average |

# 1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of chlorobenzene (CAS No. 108-90-7) are as follows:

| | |
|---|---|
| Chemical class: | monocyclic aromatic (purgeable aromatic) |
| Molecular weight: | 112.56 |
| Vapor pressure: | 11.7 mm Hg at 20°C (Mabey et al., 1981) |
| Water solubility: | 466.3 mg/ℓ at 20°C (Horvath, 1982) |
| Octanol/water partition coefficient: | 692 (Hansch and Leo, 1981) |
| Soil mobility (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%): | 1.9 (Wilson et al., 1981) |
| BCF: | 45.7 (Rainbow trout (muscle); Salmo gairdneri) (Branson, 1978) |
| | 446.7 (Fathead minnow; Pimephales promelas) (Veith et al., 1979) |
| Half-lives in Air: | 3.5 days (Kanno and Nojima, 1979) |
| Water: | 0.3 days in river (Zoeteman et al., 1980) |

The half-life of chlorobenzene in soil could not be located in the available literature; however, evaporation is expected to be the predominant loss mechanism from the soil surface (Wilson et al., 1981). The halflife for soil evaporation should be longer than its evaporation half-life from water. In subsurface soil, a fraction of monochlorobenzene may undergo biodegradation, and a fraction may leach through the soil (Wilson et al., 1981).

## 2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

### 2.1. ORAL

Quantitative studies regarding absorption of chlorobenzene in humans or laboratory animals following ingestion were not located in the available literature. Reports of toxic effects in humans following ingestion or inhalation (Reich, 1934; Rosenbaum et al., 1947; Tarkhova, 1965) suggested absorption by these routes. Deichmann (1981) reported that chlorobenzene absorption from the gastrointestinal tract was facilitated by ingestion of fats and oils. Studies of the metabolism of chlorobenzene in several mammalian species indicated that absorption from the gastrointestinal tract occurred readily (Williams, 1959).

### 2.2. INHALATION

No quantitative studies regarding absorption in humans or experimental animals following inhalation exposure to chlorobenzene could be located in the available literature. Deichmann (1981) stated that chlorobenzene was absorbed rapidly from the lungs. No supporting data accompanied this statement.

## 3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

### 3.1. SUBCHRONIC

3.1.1. Oral. No reports of subchronic oral exposure of humans to chlorobenzene could be located in the available literature. Table 3-1 summarizes pertinent subchronic oral exposure data in laboratory animals. Most of these data were taken from summaries provided by Deichmann (1981) and U.S. EPA (1980b, 1985). The studies reviewed by these authors seemed to define similar NOELs: Monsanto Company (1967a) found no effects in dogs exposed by capsule to 27.3 mg/kg/day. Following dietary exposure for 93-99 days, no effects were reported in rats at 50 mg/kg/day (Monsanto Company, 1967b), although slight and inconstant elevated liver and kidney weights were reported at this level in the published version of this study (Knapp et al., 1971). Irish (1963) found no effects in rats given 14.4-18.8 mg/kg/day, 5 days/week, for 192 days.

A study by Varshavskaya (1967) described CNS, liver, hematopoietic and endocrine effects in groups of seven male rats exposed to 0.01 and 0.1 mg chlorobenzene/kg/day by gavage. The U.S. EPA (1980b) considered the results of Varshavskaya (1967) to be questionable primarily because these data suggested effects at dosages far lower than those indicated by other investigators (Table 3-1). Also, data generated by Hollingsworth et al. (1956) in a similar study of the toxicity of o-dichlorobenzene indicated similar effects, but were associated with dosages >3 orders of magnitude greater than those reported by Varshavskaya (1967).

The NTP (1983) conducted 13-week range-finding studies in groups of five male and five female rats and mice with chlorobenzene administered by gavage. Both species were treated with 60, 125, 250, 500 or 750 mg/kg on 5 days/week (transfomed doses 42.9, 89.3, 178.6, 357 and 538 mg/kg bw/day).

TABLE 3-1

Subchronic Oral Toxicity of Chlorobenzene in Experimental Animals

| Species | Dose (mg/kg/day) | Duration (days) | Effects | Reference |
|---|---|---|---|---|
| Dogs (4M, 4F) | 27.3 | 90 | none | Monsanto Company, 1967a; Knapp et al., 1971 |
| | 54.6 | 90 | diarrhea and vomiting; conjunctivitis | |
| | 272.5 | 90 | mortality 4/8 in 3-5 weeks; increased immature leukocytes, SGOT, bilirubin, cholesterol; decreased blood sugar; histopathological changes in liver, kidneys, spleen | |
| Rats | 12.5 or 50 | 93-99 | none | Monsanto Company, 1967b |
| | 100 | 93-99 | increased liver and kidney weights | |
| | 250 | 93-99 | increased liver and kidney weights; retarded growth in males | |
| Rats | 14.4 | 192 | none | Irish, 1963 |
| | 144 and 288 given 5 days/ week | 192 | increased liver, kidney weights, salivation; partial alopecia | |

TABLE 3-1 (cont.)

| Species | Dose (mg/kg/day) | Duration (days) | Effects | Reference |
|---|---|---|---|---|
| Rats | 12.5 | 93-99 | none | Knapp et al., 1971 |
| | 50 or 100 | 93-99 | increased liver and kidney weights | |
| | 250 | 93-99 | increased liver and kidney weights, retarded growth in males | |
| Mouse | 42.9 | 13 weeks | one male with hepatic necrosis | NTP, 1983 |
| | 89.3 | 13 weeks | increased liver weights in males; one male with hepatic necrosis | |
| | 178.6 | 13 weeks | >50% reduction in weight gain, increased excretion of coproporphyrins in females, increased liver weights, lesions of the liver, kidney, bone marrow, spleen and thymus | |
| | 357 | 13 weeks | 100% lethal to males within 1 week, reduced body weight gains, polyuria in females, increased liver weights, lesions of the liver, kidney, bone marrow, spleen and thymus | |
| | 538 | 10 weeks | 100% lethal to males within 1 week and to female mice within 10 weeks, lesions of the liver, kidney, bone marrow, spleen and thymus at death | |

In mice, 100% lethality to males within 1 week occurred at ≥500 mg/kg, accompanied by histopathological lesions in many organs. All females in the 750 mg/kg group died by week 10. A 50% reduction in body weight gain and histopathological lesions were noted at 250 mg/kg. Increased liver weights in males were noted at 125 mg/kg and liver necrosis was noted in 1 male in the 125 and 1 male in the 60 mg/kg group. Male mice appeared to be affected more severely than females.

In rats, decreased body weight gain in both sexes, altered serum biochemistries in females and histopathological alterations were observed at 500 and 750 mg/kg. Decreased survival was observed at 750 mg/kg. The only effect reported at 250 mg/kg was minimal centrolobular hepatocellular necrosis. No effects were observed at the two lowest levels.

3.1.2. Inhalation. No studies regarding subchronic inhalation exposure of humans to chlorobenzene could be located in the available literature. Because of the potential for being long-term, reports of occupational exposure are discussed in Section 3.2.2.

Several studies of subchronic inhalation exposure of laboratory animals to chlorobenzene have been reviewed by Deichmann (1981) and U.S. EPA (1985) and are summarized in Table 3-2. Dilley (1977) demonstrated small, focal lesions in the adrenal cortex and kidney tubules and decreased SGOT in rats exposed to 75 ppm chlorobenzene 7 hours/day, 5 days/week for 120 days. This dosage, corresponding to an intake of 53 mg/kg/day, defined a LOAEL in rats from inhalation exposure to chlorobenzene. In an earlier study, no effects were seen in rats exposed to 142 mg/kg bw/day for 44 days (Irish, 1963).

Several reports from the foreign literature indicate effects in rats at exposures leading to dosages far below those associated with no effects in

TABLE 3-2

Subchronic Inhalation Toxicity of Chlorobenzene in Experimental Animals

| Species | Exposure | Dose[a] (mg/kg/day) | Duration (days) | Effects | Reference |
|---|---|---|---|---|---|
| Rats | 200 ppm, 7 hours/day, 5 days/week | 142 | 44 | none | Irish, 1963 |
| | 475 and 1000 ppm, 7 hours/day, 5 days/week | 338 and 713 | 44 | increasing severity of hepatomegaly, histopathological changes | |
| Rats | 0.75, 1.50 or 2 mg/ℓ 6 hours/day, 5 days/week | 99, 199 or 265 | 87 | none | Monsanto Company, 1978 |
| Rats | 0.1 or 1.0 mg/m³ continuous | 0.7 or 7.0 | 72-80 | liver necrosis and regenerations; kidney hyperplasia, encephalopathy, pneumonia | Khanin, 1977 |
| Rats | 0.1 mg/m³ continuous | 0.07 | 60 | none | Tarkhova, 1965 |
| | 1.0 mg/m³ continuous | 0.7 | 60 | inhibited chronaxia of antigonistic muscles at 39 days; increased blood cholinesterase | |
| Rats | 0.1, 1.25 or 1.5 mg/ℓ[b] | ND | 49-98 | chronaximetric inhibition | Pislaru, 1960 |
| Rats | 0.1 mg/ℓ, 3 hours/day every other day | 4.6 | 259 | inhibition of extensor tibialis at 7-14 weeks, normal by 20 weeks | Gabor and Raucher, 1960 |
| Rats | 75 or 250 ppm 7 hours/day, 5 days/week | 53 or 178 | 120 | focal lesions in adrenal cortex and and kidney tubules; congestion of liver and kidney, decreased SGOT | Dilley, 1977 |
| Rabbits | 75 or 250 ppm, 7 hours/day, 5 days/week | 102 or 340 | 120 | decreased SGOT | Dilley, 1977 |
| Rabbits | 200 ppm, 7 hours/day, 5 days/week | 271 | 44 | none | Irish, 1963 |
| Guinea pigs | 200 ppm, 7 hours/day, 5 days/week | 102 | 44 | none | Irish, 1963 |

TABLE 3-2 (cont.)

| Species | Exposure | Dose[a] (mg/kg/day) | Duration (days) | Effects | Reference |
|---|---|---|---|---|---|
| Dogs | 0.75 mg/ℓ, 6 hours/day, 5 days/week | 15.8 | 87 | none | Monsanto Company, 1978 |
| | 1.50 mg/ℓ, 6 hours/day, 5 days/week | 31.6 | 87 | weight loss, conjunctivitis, moribund by 31 days | |
| | 200 mg/ℓ, 6 hours/day, 5 days/week | 4218 | 87 | weight loss, hypoactivity and conjunctivitis; vacuolated hepatocytes, cytoplasmic vacuolation of renal tubules, bilateral atrophy of seminiferous tubules; leukocytopoenia; elevated SAP, SGOT, SGPT; aplastic bone marrow, mortality in 5/8 dogs by 25-29 days | |

[a]Dose in mg/kg was calculated assuming the following inhalation rates and body weights: rats - 0.26 m³/day and 0.35 kg; rabbits - 1.6 m³/day, 1.13 kg; guinea pigs - 0.23 m³/day, 0.43 kg; dogs - 1.5 m³/day, 12.7 kg

[b]Exposure data insufficient for calculation of dose

ND = Not derived because exposure data are insufficient

reports from the domestic literature. For example, Khanin (1977) reported histopathological lesions in several organs at 0.7 mg/kg bw/day. Neuromuscular dysfunction was reported in rats at exposures leading to dosages of 0.7-4.6 mg/kg bw/day (Tarkhova, 1965; Pislaru, 1960; Gabor and Raucher, 1960). In the absence of corroborating evidence from the domestic literature, the data are not considered reliable for use in risk assessment.

In subchronic inhalation experiments in other species, no adverse effects were observed in rabbits at 102-340 mg/kg bw/day (Dilley, 1977; Irish, 1963), in guinea pigs at 102 mg/kg bw/day (Irish, 1963) or in dogs at 15.8 mg/kg bw/day (Monsanto Company, 1978). Dogs appear to be the most sensitive species tested, however, as weight loss and moribundity occurred in this species by 31 days of exposure to 31.6 mg/kg bw/day (Monsanto Company, 1978).

3.2. CHRONIC

3.2.1. Oral. No reports of chronic oral exposure of humans to chlorobenzene could be located in the available literature. Minimal toxicity data are available from the 103-week carcinogenicity bioassay in rats and mice (NTP, 1983). Groups of 50 male and 50 female B6C3F$_1$ mice were treated by gavage with chlorobenzene in corn oil at 0, 60 and 120 mg/kg for females and 0, 30 and 60 mg/kg for males. Groups of 50 male and 50 female F344/N rats were treated with 0, 60 and 120 mg/kg. Treatments were performed 5 days/week for 103 weeks. Both untreated and vehicle-treated controls were maintained.

Neither mice nor rats had clinical signs of toxicity related to treatment with chlorobenzene. Statistically significant reduced survival was observed in low-dose male mice and high-dose male rats. Increased body weights in both treated groups of female rats were noted during the second

year of the experiment. No histopathologic evidence of toxicity was was observed in mice; however, rats had "equivocal evidence for mild chlorobenzene-induced hepatocellular necrosis."

**3.2.2. Inhalation.** The only available reports of chronic human exposure to monochlorobenzene were summaries by U.S. EPA (1985) and Deichmann (1981), from which this discussion was adapted. Girard et al. (1969) reported the case of a 70-year-old woman exposed for 6 years to a glue containing 70% chlorobenzene. From the time she began using the glue, she experienced headaches and irritation of the mucosa of the upper respiratory tract and eyes. After 6 years, she had developed medullary aplasia. No exposure data were available.

Rosenbaum et al. (1947) examined 28 factory workers, many of whom complained of headaches and showed signs of somnolescence and dyspepsia. Other complaints included tingling, numbness and stiffness of the extremities (8 workers), hyperesthesia of the hands (4 workers), and spastic contractions of the finger muscles (9 workers) or of the gastrocnemius (2 workers). These workers had reportedly been exposed for 1-2 years, but details of exposure were not specified. No neurotoxic signs were displayed by 26 workers exposed to benzene and/or chlorobenzene fumes for <1 year.

No reports of chronic inhalation exposure of laboratory animals to chlorobenzene could be located in the available literature.

## 3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

No reports of fetotoxicity or teratogenicity in humans or animals associated with either oral or inhalation exposure to chlorobenzene could be located in the available literature.

## 3.4. TOXICANT INTERACTIONS

No pertinent data confirming the interaction of chlorobenzene with other xenobiotics could be located in the available literature. Generalizing that the halogenated benzenes appeared to increase the activity of microsomal cytochrome P-450-dependent enzyme systems, the U.S. EPA (1980b) suggested that exposure to chlorobenzene might be expected to hasten metabolism of other xenobiotics to either more or less toxic metabolites.

Shelton and Weber (1981) investigated the hepatotoxicity of a 1:38 molar ratio mixture of carbon tetrachloride and chlorobenzene in male CF-1 mice. The dosages used (not specified) were given by intraperitoneal injection. Although parameters of hepatotoxicity were not mentioned, the U.S. EPA (1985) stated that the dose-response did not deviate from that predicted by addition alone.

## 4. CARCINOGENICITY

### 4.1. HUMAN DATA

No reports associating chlorobenzene with cancer in humans could be located in the available literature.

### 4.2. BIOASSAYS

The NTP (1983) conducted a study of the carcinogenicity of chlorobenzene in rats and mice. Based on data from a 13-week dose range-finding experiment, 50 rats of each sex were treated by gavage with 60 or 120 mg/kg, 5 days/week for 103 weeks. Both untreated and vehicle-treated control groups of 50 rats of each sex were maintained.

Throughout the study, body weight of treated and control animals remained comparable. Survival rates were similar until about 70 weeks of treatment, at which time survival in high-dose group males was significantly reduced. Survival at the end of 2 years was 68, 78, 64 and 52% in untreated control, vehicle-treated control, low-dose and high-dose males, respectively. Among female rats, 2-year survival data were 74, 58, 60 and 62% in untreated control, vehicle-treated control, low-dose and high-dose groups, respectively.

Although there was some disagreement in the interpretation of liver lesions, pathologists evaluating the slides seemed to agree that inflammation and cytoplasmic basophilia, manifestations of hepatic degeneration, were less severe in chlorobenzene-treated rats than in the control groups. In male rats, a significant increase in neoplastic nodules in the liver was observed in the high-dose group (Table 4-1) as determined by both the incidental tumor test ($p=0.021$) and the Cochran-Armitage test for dose-related trend ($p=0.043$). Liver carcinomas in male rats were found only in the vehicle-treated group (2/50). Combining the incidences of neoplastic

TABLE 4-1

Statistical Comparisons of Liver Tumors in Male Rats
Treated with Chlorobenzene*

| Tumor Type | Untreated Control | Vehicle Control | 60 mg/kg | 120 mg/kg |
|---|---|---|---|---|
| Neoplastic nodule | 4/50 (8%) | 2/50 (4%) | 4/49 (8%) | 8/49 (16%) |
| Incidental tumor test | | p=0.011 | p=0.290 | p=0.021 |
| Cochran-Armitage test | | p=0.027 | NA | NA |
| Fisher exact test | | NA | p=0.329 | p=0.043 |
| Carcinoma | 0/50 (0%) | 2/50 (4%) | 0/49 (0%) | 0/49 (0%) |
| Incidental tumor test | | p=0.139 | p=0.283 | p=0.331 |
| Cochran-Armitage test | | p=0.098 | NA | NA |
| Fisher exact test | | NA | p=0.253 | p=0.253 |
| Neoplastic nodule or carcinoma | 4/50 (8%) | 4/50 (8%) | 4/49 (8%) | 8/49 (16%) |
| Incidental tumor test | | p=0.054 | p=0.570 | p=0.083 |
| Cochran-Armitage test | | p=0.121 | NA | NA |
| Fisher exact test | | NA | p=0.631 | p=0.168 |

*Source: NTP, 1983

NA = Not applicable

nodules and carcinomas failed to create an overall tumor incidence that was statistically significant. There was no evidence of neoplastic nodule or liver tumor formation in female rats.

The incidence of pituitary tumors (adenoma, adenocarcinoma and carcinoma) in both male and female rats was found to be significantly inversely related to treatment with chlorobenzene (Table 4-2).

The carcinogenicity of chlorobenzene has also been tested in $B6C3F_1$ mice (NTP, 1983). Males were treated with 30 or 60 mg/kg and females were subjected to 60 or 120 mg/kg, 5 days/week for the 2-year (103-week) treatment period. These dosages were chosen on the basis of a preliminary 13-week dose range-finding study. It appeared that the doses chosen for the chronic bioassay were too low based on the data generated by the 13-week preliminary study, and that the accepatable intake had not been approached (U.S. EPA, 1985). No tumors occurred with frequencies that differed significantly from those in the control groups.

The U.S. EPA (1985) stated that the data generated by these studies were not sufficient to draw conclusions about the carcinogenicity of chlorobenzene.

## 4.3. OTHER RELEVANT DATA

Studies of the mutagenicity of chlorobenzene in microorganisms have yielded mixed results, with positive results observed only in tests with Saccharomyces cerevisiae (Simmon et al., 1979) and Streptomyces antibioticus (Keskinova, 1968) (Table 4-3).

In a sex-linked recessive lethal test in Drosophila melanogaster (Bioassay Systems Corp., 1982), male flies were exposed to 36,000 or 128,400 ppm of chlorobenzene for 1 hour. The exposed flies were mated at 1-3 days

TABLE 4-2

Pituitary Tumors in Male Rats Treated with Chlorobenzene*

| Tumor Type | Untreated Control | Vehicle Control | 60 mg/kg | 120 mg/kg |
|---|---|---|---|---|
| Adenoma | 20/49 (41%) | 10/50 (20%) | 9/42 (21%) | 3/47 (6%) |
| Incidental tumor test | | p=0.109 | p=0.532 | p=0.101 |
| Cochran-Armitage test | | p=0.047 | NA | NA |
| Fisher exact test | | NA | p=0.534 | p=0.046 |
| Adenoma, adenocarcinoma or carcinoma | 20/49 (41%) | 12/50 (24%) | 9/42 (21%) | 3/47 (6%) |
| Incidental tumor test | | p=0.044 | p=0.462 | p=0.044 |
| Cochran-Armitage test | | p=0.016 | NA | NA |
| Fisher exact test | | NA | p=0.484 | p=0.015 |

*Source: NTP, 1983

NA = Not applicable

TABLE 4-3

Mutagenicity Testing of Chlorobenzene*

| Test System | Metabolic Activation | Concentration | Result | Reference |
|---|---|---|---|---|
| Asperigillus nidulans | - | 200 µg/mℓ | negative | Prasad, 1970 |
| Salmonella strains TA1535, TA1537, TA1538, TA92, TA98, TA100 | ± | 0.1-0.5 µℓ/plate | negative | Simmon et al., 1979 |
| Salmonella typhimurium strains | ± | 100 µg/plate | negative | Merck and Company, 1978 |
| Saccharomyces cerevisiae | ± | 0.05-6% | positive | Simmon et al., 1979 |
| S. cerevisiae | ± | 0.01-5 µℓ/plate | negative | Monsanto Company, 1976 |
| Mouse lymphoma L5178Y (forward mutation of TK) | -<br>+ | 0.001-0.1 µℓ/mℓ<br>0.0001-0.01 µℓ/mℓ | negative<br>negative | Monsanto Company, 1976 |
| Escherichia coli ($polA^+/polA^-$) | - | 10-20 µℓ/plate | negative | Simmon et al., 1979 |
| Bacillus subtilis ($rec^-/rec^+$) | - | 10-20 µℓ/plate | negative | Simmon et al., 1979 |
| Streptomyces antibioticus | - | NR | positive | Keskinova, 1968 |

*Source: U.S. EPA, 1985

NR = Not reported

(to sample effects on spermatozoa), 4-5 days (to sample effects on spermatids) and 6-7 days (to measure effects on spermatocytes) after exposure. No evidence of mutagenicity was found in 11,543 chromosomes from treated flies compared to 9430 chromosomes from control flies.

A positive response was obtained in a test for *in vitro* induction of chromosomal aberrations in Chinese hamster ovary cells (U.S. EPA, 1982b). Concentrations of 444, 266 and 178 µg/mℓ were tested in assays not incorporating a metabolic activating system and concentrations of 493, 296, 197 and 99 µg/mℓ were assayed with an S-9 activating system. A positive response was observed in the S-9 activated system after a 4-hour exposure but not after a 2-hour exposure.

### 4.4. WEIGHT OF EVIDENCE

No evidence of carcinogenicity associated with exposure to chlorobenzene in humans could be located in the available literature. The NTP (1983) bioassay failed to confirm or deny the carcinogenicity of chlorobenzene in rats or mice. IARC has not evaluated the risk to humans associated with oral or inhalation exposure to chlorobenzene. By applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating the overall weight of evidence for carcinogenicity to humans (Federal Register, 1984), a designation of chlorobenzene as a Group D - Not Classified chemical seems most appropriate.

## 5. REGULATORY STANDARDS AND CRITERIA

A summary of regulatory standards and criteria for chlorobenzene is presented in Table 5-1. Both the ACGIH (1980) and NIOSH (1982) have set the TWA for chlorobenzene at 75 ppm. No STEL has been set.

The U.S. EPA (1980b) has suggested an ambient water quality criterion of 488 µg/ℓ to protect human health. This criterion is based on an ADI of 1.008 mg/day, assumes consumption of 2 ℓ water/day and takes into consideration consumption by fish and shellfish.

TABLE 5-1

Current Regulatory Standards and Criteria for Chlorobenzene

| Standard or Criterion | Value | Reference |
|---|---|---|
| TLV | 75 ppm (~350 mg/m³) | ACGIH, 1980 |
| TWA | 75 ppm | U.S. EPA, 1985 |
| Ambient water quality criteria: | | |
| Freshwater aquatic life | | |
| Acute toxicity | 250 µg/ℓ | U.S. EPA, 1985 |
| Saltwater aquatic life | | |
| Acute toxicity | 160 µg/ℓ | U.S. EPA, 1985 |
| Chronic toxicity | 129 µg/ℓ | U.S. EPA, 1985 |
| Ambient water quality criterion: | | |
| Human life | 488 µg/ℓ | U.S. EPA, 1985 |
| Organoleptic | 20 µg/ℓ | U.S. EPA, 1985 |

## 6. RISK ASSESSMENT

### 6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. NOAELs from subchronic oral studies include 14.4 mg/kg/day in rats (Irish, 1963), 50 mg/kg/day in rats (Monsanto Company, 1967b), 89.3 mg/kg/day in rats (125 mg/kg, 5 days/week) (NTP, 1983), 12.5 mg/kg/day in rats (Knapp et al., 1971) and 27.3 mg/kg/day in dogs (Monsanto Company, 1967a; Knapp et al., 1971). The Irish (1963) study reported a NOEL of 14.4 mg/kg/day and LOAEL of 144.4 mg/kg/day, however, intermediate doses were not evaluated. The Monsanto (1967a,b) study defined a NOAEL of 50 mg/kg/day and LOAEL of 100 mg/kg/day in the rat. In contrast, a NOEL of 27.3 mg/kg/day and a LOAEL of 55 mg/kg/day were defined for the dog. The observed adverse effects indicated a higher sensitivity of the dog to chlorobenzene than the rat. Based on these findings the highest dog NOEL of 27.3 mg/kg/day (Monsanto, 1967b) was considered appropriate to derive an ADI for subchronic exposure. An uncertainty factor of 100 is applied, a factor of 10 to account for interspecies extrapolation and a factor of 10 to provide greater protection for especially sensitive populations. Assuming a body weight in man of 70 kg, an AIS for man can be calculated as follows:

$$\text{AIS} = (27.3 \text{ mg/kg/day days} \times 70 \text{ kg}) \div 100$$
(the uncertainty factor derived above)

$$\text{AIS} = 19.1 \text{ mg/day}$$

In dogs immature leukocytes, low blood sugar, conjunctivitis, vomiting and diarrhea were reported at 55 mg/kg/day, whereas higher doses caused mortality and histopathological lesions in liver and kidneys (Monsanto, 1967a). A human MED was calculated by multiplying the dog MED by the cube root of the ratio of the body weight of dogs (assumed: 12.7 kg) to that of humans (assumed: 70 kg) and dividing the result by 10, an uncertainty

factor chosen to reflect the unknowns in extrapolating from a subchronic study to chronic application. The result, 3.1 mg/kg/day, is multiplied by 70, resulting in an MED of 218 mg/day for a 70 kg man. This MED corresponds to an $RV_d$ of 2.0; the effects of vomiting, diarrhea, conjunctivitis and immature luekocytes rate an $RV_e$ of 4. A CS of 8, the product of $RV_d$ and $RV_e$, is calculated.

6.1.2. Inhalation. No pertinent data regarding the effects of subchronic inhalation exposure of humans to chlorobenzene could be located in the available literature. Studies by Irish (1963) defined NOELs in rats, rabbits and guinea pigs of 142, 271 and 102 mg/kg/day, respectively. Dilley (1977) found small focal lesions in the adrenal cortex and kidney tubules, congestion of the liver and kidney, and decreased SGOT in rats exposed to 75 ppm chlorobenzene for 7 hours/day, 5 days/week for 120 days. This concentration resulted in an intake of 53 mg/kg/day (applying the assumptions stated in Table 3-2), which was designated as a LOAEL in this study. An interim AIS can be calculated from these data by assuming a body weight of man of 70 kg and using an uncertainty factor of 1000; a factor of 10 to account for interspecies conversion, another factor of 10 to convert from a LOAEL to a NOEL and a final factor of 10 to afford greater protection to unusually sensitive populations. The resultant interim AIS is 3.7 mg/day.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. No reports of chronic oral exposure of humans or animals to chlorobenzene could be located in the available literature. An interim AIC for chronic oral exposure can be derived from the subchronic AIC by applying an additional uncertainty factor of 10 to convert from a subchronic study to chronic exposure; this results in an overall uncertainty factor of 1000. The resultant AIC is 1.9 mg/day.

6.2.2. Inhalation. No reports of chronic exposure of humans to chlorobenzene that were satisfactory for risk assessment, or studies of chronic animal exposure could be located in the available literature. The study by Dilley (1977), used to derive an AIS, can be used to derive an AIC for inhalation exposure. An additional uncertainty factor of 10 to account for derivation of an AIC from subchronic data results in an AIC of 0.4 mg/day, starting with the AIS of 3.7 mg/day (see Section 6.1.2).

6.3. CARCINOGENIC POTENCY ($q_1^*$)

6.3.1. Oral. The NTP (1983) bioassay failed to demonstrate conclusively the carcinogenicity, or lack of carcinogenicity, of chlorobenzene administered to rats and mice by gavage. No other reports of carcinogenicity in humans or animals resulting from oral exposure to chlorobenzene could be located in the available literature. Therefore, insufficient data are available from which to estimate carcinogenic potency.

6.3.2. Inhalation. No reports of carcinogenicity in humans or animals associated with inhalation exposure to chlorobenzene could be located in the available literature; hence, no estimation of carcinogenic postency has been made.

## 8. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air, 4th ed. Cincinnati, OH. p. 84-85. (Cited in U.S. EPA, 1982a)

Bioassay Systems Corp. 1982. Drosophilia sex-linked recessive lethal test on monochlorobenzene. U.S. EPA, Office of Pesticides and Toxic Substances, Washington, DC. TSCA Section 8(d) submission. (Cited in U.S. EPA, 1985)

Branson, D.R. 1978. Predicting the fate of chemicals in the aquatic environment from laboratory data. ASTM STP 657. American Society for Testing and Materials, Philadelphia, PA. p. 55-76.

Deichmann, W.B. 1981. Halogenated Cyclic Hydrocarbons. In: Toxicology. Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. 2B, G.D. Clayton and E.E. Clayton, Ed. John Wiley and Sons, Inc., NY. p. 3605-3611. (Cited in U.S. EPA, 1982a)

Dilley, J.V. 1977. Toxic Evaluation of Inhaled Chlorobenzene. NIOSH, DHEW, Cincinnati, OH. Contract 210-76-0126. (Cited in U.S. EPA, 1985)

Federal Register. 1984. Environmental Protection Agency. Proposed guidelines for carcinogenic risk assessment. 49 FR 46294-46299.

Gabor, S. and K. Raucher. 1960. Studien zur Bestimmung der zulassigne benzol und monochorbenzol grenzkonzentrationen. J. Hyg. Epidemiol. Microbiol. Immunol. 4: 223-231. (Ger.) (Cited in U.S. EPA, 1985)

Girard, R., F. Tolot, P. Martin and J. Bourret. 1969. Serious blood disorders and exposure to chlorine derivatives of benzene (A report of 7 cases). J. Med. Lyon. 50: 771-773. (Cited in U.S. EPA, 1985)

Hansch, C. and A.J. Leo. 1981. Medchem Project. Issue No. 19. Pomona College, Claremont, CA.

Hollingsworth, R.L., V.K. Rowe, F. Oyen, H.R. Hoyle and H.C. Spencer. 1956. Toxicity of paradichlorobenzene: Determination on experimental animals and human subjects. AMA Arch. Ind. Health. 14: 138-147. (Cited in U.S. EPA, 1980b)

Horvath, A.L. 1982. Halogenated Hydrocarbons: Solubility-Miscibility with Water. Marcel Dekker, Inc., New York, NY. p. 889.

Irish, D.D. 1963. Halogenated Hydrocarbons: II. Cyclic. In: Industrial Hygiene and Toxicology, Vol. II, 2nd ed., F.A. Patty, Ed. Interscience, NY. p. 1333-1361. (Cited in U.S. EPA, 1980b)

Kanno, S. and K. Nojima. 1979. Studies on photochemistry of aromatic hydrocarbons. V. Photochemical reaction of chlorobenzene with nitrogen oxides in air. Chemosphere. 8: 225-232.

Keskinova, D.V. 1968. The effect of dimethylcyclodiazomethane in chlorobenzene solution on mutagenesis in Actinomyces antibioticus 400. Genetika. 4(8): 121-125. (Cited in U.S. EPA, 1985)

Khanin, A.G. 1977. Pathological changes in the general nervous system and internal organs of experimental animals after chronic continuous inhalation of toxic substances. Chem. Abstr. 74: 97-106. (Cited in U.S. EPA, 1985)

Knapp, W.K., Jr., W.M. Busey and W. Kundzins. 1971. Subacute oral toxicity of monochlorobenzene in dogs and rats. Toxicol. Appl. Pharmacol. 19: 393. (Abstr.) (Cited in U.S. EPA, 1980b)

Mabey, W.R., J.H. Smith and R.T. Podoll. 1981. Aquatic Fate Process Data for Organic Priority Pollutants. Monitoring and Data Support Division, Office of Water Regulations and Standards, Washington, DC. EPA 440/4-81-014.

Merck and Company. 1978. Summary of Monochlorobenzene Bacterial Mutagen Test (Ames Test). Office of Pesticides and Toxic Substances, U.S. EPA, Washington, DC. TSCA Sec 8(d) submission 8DHQ-1078-0302. (Cited in U.S. EPA, 1985)

Monsanto Company. 1967a. 13-Week oral administration - dogs, monochlorobenzene. U.S. EPA, OPTS, Washington. DC. TSCA Sec 8(d) submission 8DHQ-1078-0202(2). (Cited in U.S. EPA, 1985)

Monsanto Company. 1967b. 3-Month subacute oral study of monochlorobenzene in rats. U.S. EPA, Washington. DC. TSCA Sec 8(d) submission 8DHQ-1078-Q212(3). (Cited in U.S. EPA, 1985)

Monsanto Company. 1976. Litton Bionetics mutagenicity evaluation of Bio-76-86-CP 5535 (WGK): Monochlorobenzene. Office of Pesticides and Toxic Substances, U.S. EPA, Washington, DC. TSCA Sec 8(d) submission 8DHQ-1078-0214(1). (Cited in U.S. EPA, 1985)

Monsanto Company. 1978. Industrial Bio-Test draft report of 90-day subacute vapor inhalation toxicity study with monochlorobenzene in beagle dogs and albino rats. U.S. EPA, OPTS, Washington, DC. TSCA Sec 8(d) submission 8DHQ-1078-0202(1). (Cited in U.S. EPA, 1985)

NIOSH (National Institute for Occupational Safety and Health). 1972. The 1982 Registry of Toxic Effects of Chemical Substances, R.L. Lewis and R.L. Tatken, Ed. Cincinnati, OH. (Cited in U.S. EPA, 1985)

NTP (National Toxicology Program). 1983. Carcinogenesis studies of chlorobenzene (CAS No. 108-99-7) in F344/N rats and B6C3F1 mice (gavage studies). NTP-82-90. NIH Publ. 83-2517. (Draft)

Pislaru, V. 1960. Modificari cronaximetrice in intoxicatia cronica cu benzen si monochlorobenzen. Igiena. 9: 127-135. (Cited in U.S. EPA, 1985)

Prasad, I. 1970. Mutagenic effects of the herbicide 3',4'-dichloropropionanilide and its degradation products. Can. J. Microbiol. 16: 369-372. (Cited in U.S. EPA, 1985)

Reich, H. 1934. Puran (Monochlorobenzol)-Vergiftung bei einem zweijahrigen Kinde. Vergiftungsfalle. 5: 193-194. (Ger.) (Cited in U.S. EPA, 1985)

Rosenbaum, N.D., R.S. Block, S.N. Kremneva, S.L. Ginzburg and I.V. Pozhariskii. 1947. The use of chlorobenzene as a solvent from the point of view of industrial hygiene. Gig. Sanit. 12(1): 21-24. (Cited in U.S. EPA, 1985)

Shelton, D.W. and L.J. Weber. 1981. Quantification of the joint effects of mixtures of hepatotoxic agents: Evaluation of a threshold model in mice. Environ. Res. 26: 33-41. (Cited in U.S. EPA, 1985)

Simmon, V.F., E.S Riccio and M.V. Peirce. 1979. In vitro microbiological genotoxicity assays of chlorobenzene, m-dichlorobenzene, o-dichlorobenzene and p-dichlorobenzene. Contract No. 68-02-2947. U.S. EPA, ORD, Washington, DC. (Cited in U.S. EPA, 1985)

Tarkhova, L.P. 1965. Maximum permissible concentration of chlorobenzene in the atmosphere. Gig. Sanit. 30: 8. (Cited in U.S. EPA, 1985)

U.S. EPA. 1980a. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria. Federal Register. 45:79347-79357.

U.S. EPA. 1980b. Ambient Water Quality Criteria for Chlorinated Benzenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-028. NTIS PB 81-117392.

U.S. EPA. 1982a. Hazard Profile for Chlorobenzene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1982b. Effects of Monochlorobenzene on the in vitro Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells. Prepared for U.S. EPA by Bioassay Systems Corp. (Cited in U.S. EPA, 1985)

U.S. EPA. 1983. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Health Assessment Document for Chlorinated Benzenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-015F. NTIS PB 85-150332.

Varshavskaya, S.P. 1967. Comparative toxicological characteristics of chlorobenzene and dichlorobenzene (ortho- and para-isomers) in relation to the sanitary protection of water bodies. (Rus. trans.) Hyg. San. 33(10): 17-23. (Cited in U.S. EPA, 1980b)

Veith, G.D., D.L. DeFoe and B.V. Bergstedt. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. J. Fish Res. Board Can. 36: 1040-1048.

Williams, R.T. 1959. The Metabolism of Halogenated Aromatic Hydrocarbons. Detoxication of Mechanisms, 2nd ed. John Wiley and Sons, Inc., NY. p. 237. (Cited in U.S. EPA, 1985)

Wilson, J.T., C.G. Enfield, W.J. Dunlap, R.L. Cosby, D.A. Foster and L.B. Baskin. 1981. Transport and fate of selected organic pollutants in a sandy soil. J. Environ. Qual. 10: 501-506.

Zoeteman, B.C.J., K. Harmsen, J.B.H.J. Linders, C.F.H. Morra and W. Slooff. 1980. Persistent organic pollutants in river water and groundwater of The Netherlands. Chemosphere. 9: 231-249.

## APPENDIX

Summary Table for Chlorobenzene

| | Species | Experimental Dose/Exposure | Effect | Acceptable Intake (AIS or AIC) | Reference |
|---|---|---|---|---|---|
| Inhalation | | | | | |
| AIS | rat | 53 mg/kg/day | focal lesions in liver, kidney tubules; hepatic and renal congestion; decreased SGOT | 3.7 mg/day | Dilley, 1977 |
| AIC | rat | 53 mg/kg/day | focal lesions in liver, kidney tubules; hepatic and renal congestion; decreased SGOT | 0.4 mg/day | Dilley, 1977 |
| Oral | | | | | |
| AIS | dog | 27.3 mg/kg/day for 90 days | none | 19.1 mg/day | Monsanto, 1967a |
| AIC | dog | 27.3 mg/kg/day for 90 days | none | 1.9 mg/day | Monsanto, 1967a |
| Maximum composite score | dog | 55 mg/kg/day for 90 days ($RV_d$ = 2.0) | immature leukocytes, conjunctivitis, vomiting and diarrhea ($RV_e$=4) | 8 | Monsanto, 1967a |

ND = Not derived